REMARKS

Claims 1, 6-9, 12-14, 19, 26-27, 33 and 38-41 are pending in the present application. Claim 1 has been amended to recite Formula Ib and Formula II from previous claim 18. Claim 1 and other claims have also been corrected with respect to the substituent "-$OSO_3\underline{H}$" which is a clear error easily recognized by one skilled in the art. Support for new claims 38-42 is found in original claims 20, 28, 35 and 36, respectively.

Unity of Invention and Election Requirements

Applicant respectfully maintains a traversal of the Unity of Invention and Election of Species Requirements as modified in the Office Action of May 29, 2009 for essentially the same reasons stated in the Response filed April 1, 2009. The asserted basis for this Requirement apparently still rests on the assumption that the cited Bellini et al. reference (European Journal of Medicinal Chemistry, Vol. 18, No. 2, 1983, pp. 185-190) discloses one or more of the claimed compounds. However, Bellini et al. fails to disclose any of the compounds falling within the scope of the presently amended claims since none of the Bellini et al. compounds contains a R2 and/or R11 moiety having at least one free NH_2 group as recited in the present claims. Also, the compounds of Bellini et al. having a cholanoic acid backbone are even further distinguished from those within the scope of the present claims. It is also noted that compound 101 is now covered by: pending claims 1, 2, 6, 7, 12, 14, 26, 27, 33, and 37, as well as new claims 38-41.

Priority Information

Applicant has amended the specification to correction indicate the priority information in response to the comments at pages 3-5 of the Office Action of May 29, 2009.

Objection to the Specification

The specification has been objected to due to the use of the trademark "Fucidin". The specification has been amended to indicate this term in all capital letters such that this objection should be withdrawn.

Issues under 35 USC 112, First Paragraph

Claim 33 has been rejected under 35 USC 112, first paragraph, for failing to satisfy the enablement requirement because of the recitation of the term "preventing". Claim 33 has been amended so as to remove this term. It is submitted that the basis for this rejection has been removed such that the rejection should now be withdrawn.

Issues under 35 USC 112, Second Paragraph

Claim 1 has been rejected under 35 USC 112, second paragraph, as allegedly being indefinite. It is noted that in the definition of R2 and R11 the proviso has been left out because it became redundant in view of the other claim changes. It is submitted that presently amended claim 1 contains no "indefinite" terms with respect to the definitions of R2 or R11. In claim 1 it is recited that "... R2 and/or R11 represents a moiety of the formula ...(11 specific moieties listed)". That is, either R2 or R11 or both must represent one of the listed moieties. For example, if R2 represents one of the 11 moieties claimed, R11 may be $-(Z)_n-(NR-Z)_p-N(R)_2$ in the broader definition as defined in claim 1. Therefore, it is respectfully requested that the above rejection be withdrawn.

Issues under 35 USC 103(a)

Claims 1, 2, 6, 7, 26, 27, 33 and 37 have been rejected under 35 USC 103(a) as being unpatentable over Lee et al. (J. Cont. Rel. 22, 223-37, 1992) in view of Mintz '453 '453 (US 5,744,483

These rejections are traversed based on the reasons below.

Distinctions over Cited References

The compounds of presently amended claim 1 now recite formula Ib, and represent branched polyamine fusidic acid derivatives with a fusidic acid backbone - being distinct from a "normal steroid" backbone - and which are characterised by a saturated tetracyclic nucleus with a

characteristic overall chair/boat/chair conformation which is defined by the fixed stereochemistry of the carbon atoms C14, C8, C5, C19, C9 (according to steroid numbering) to which R5, R6, R9, R14, and R15 respectively are attached. Fusidic acid is not a steroid in the normal sense since it belongs to the fusidanes which is a small family of naturally occurring antibiotics having in common a tetracyclic ring system with a unique chair-boat-chair conformation separating them from typical steroids.

Mintz '453 is directed to typical or "normal" steroids, i.e. cholane and deoxycholane derivatives. Mintz '453 fails to disclose or suggest any of the presently claimed and differently shaped fusidic acid compounds of the present invention. The different three-dimensional structure makes it very difficult to predict with any degree of certainty whether any modifications to the steroid backbone described in Mintz '453 would be effective if made to a fusidic acid backbone contained within the presently claimed compounds. Consequently, significant patentable distinctions exist over Mintz '453.

Lee et al. discloses12 individual fusidic acid derivative compounds with different surfactant properties which are synthesized and tested for their ability as enhancers for mucosal permeation, i.e. as a carrier that mediates permeability changes of proteins and peptides in the nasal mucosa. Lee et al. fails to disclose or suggest any of the presently claimed compounds, such that significant patentable distinctions exist over this reference.

Lee et al. cannot be combined in any reasonable or meaningful way with Mintz '453 in an attempt to obtain the compounds of the present invention. While Lee et al. is directed to a small group of fusidic acid derivatives investigated for penetration enhancing properties, Mintz '453, on the other hand, is directed to a group of cholanoic acid derivative compounds used as antibiotics.

A person of ordinary skill in the art would not consider linking Lee et al. describing tests of 12 individual fusidic acid derivatives for their use as penetration enhancing agents with Mintz '453 describing cholanoic acid derivatives which may be used as drugs for treating antibacterial infections. To the best of Applicant's knowledge none of the 12 fusidic acid derivatives tested in Lee et al. have been suggested for or used in treatment of antibacterial infections, such that these derivatives should not be characterized as having "established antimicrobial activity" as

mentioned in the Office Action. In fact, Lee et al. mentions at page 236, line 1-4 that, "...The conclusion that mucosal erosion is not a significant factor in the fusidate mediated enhancement process is not meant to imply that these or other surfactants are harmless to the mucosa. The use of enhancers is, in fact, limited due to the unknown clinical consequences..." (emphasis added).

The Examiner states that it would have been obvious to substitute the straight chain polyamine group of fusidic acid derivatives as taught by Lee et al. with the branched polyamine compounds of Mintz '453, because Mintz '453 teaches that fusidic acid could be co-administered with the compounds disclosed in Mintz '453. Applicant respectfully disagrees for several reasons. First of all, Lee et al. is concerned with fusidic acid derivatives, whereas Mintz '453 is directed to cholanoic acid derivatives. Secondly, fusidic acid is commonly known to be effective only against Gram-positive bacteria. See the attached literature reference, Exhibit A (Antibiotic and Chemotherapy, Finch Editor, Churchill Livingstone New York, 2003, pp. 297-299). This is also emphasized in Table 1 in the present invention, where fusidic acid (FA) is tested as reference compound. Hence if one is looking for compounds having an effect against Gram-negative bacteria, the skilled person would not be led in the direction of compounds according to the present invention by being taught that a cholanoic acid derivative may be co-administrated with a specific compound mainly used against Gram-positive bacteria infections. In contrast, the present invention, in the amended claims filed with this letter, concerns fusidic acid derivatives with a branched polyamine which have a broad antimicrobial, and in particular a broad antibacterial activity both against Gram-negative and Gram positive bacteria.

The various court decisions referred to in the Office Action are all inapplicable to the present situation, as the prior art cited in connection with these decisions was directed to much more closely related compounds, both with regard to structural features and fields of use. In contrast, the compounds of Lee et al. and Mintz '453 are not structurally close and are not used for the same/related purpose.

Consequently, it is submitted that numerous significant patentable distinctions exist over both Lee et al. and Mintz '453. Also, these references cannot be combined together for several reasons as discussed above. Therefore, the above rejection must be withdrawn.

It is submitted for the reasons above that the present claims define patentable subject matter such that this application should now be placed in condition for allowance.

If any questions arise in the above matters, please contact Applicant's representative, Andrew D. Meikle (Reg. No. 32,868), in the Washington Metropolitan Area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: October 29, 2009

Respectfully submitted,

By________________________

Andrew D. Meikle
Registration No.: 32,868
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant

Exhibit A

Exhibit A

EIGHTH EDITION

Antibiotic and Chemotherapy

Anti-infective agents and their use in therapy

Edited by

Roger G. Finch
MB BS FRCP FRCPath FRCPEd FFPM
Professor of Infectious Diseases, Division of Microbiology and Infectious Diseases,
Clinical Laboratory Sciences, The City Hospital, Nottingham, UK

David Greenwood
BSc PhD DSc FRCPath
Emeritus Professor of Antimicrobial Science, Division of Microbiology and
Infectious Diseases, Department of Clinical Laboratory Sciences, University
Hospital, Queen's Medical Centre, Nottingham, UK

S. Ragnar Norrby
MD PhD FRCP (Edin)
Professor and Director General
The Swedish Institute for Infectious Disease Control, Solna, Sweden

Richard J. Whitley
MD
Loeb Scholar in Pediatrics
Professor of Pediatrics, Microbiology, Medicine and Neurosurgery
Department of Pediatrics,
The University of Alabama at Birmingham,
Birmingham, Alabama, USA

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CHAPTER

21 Fusidanes

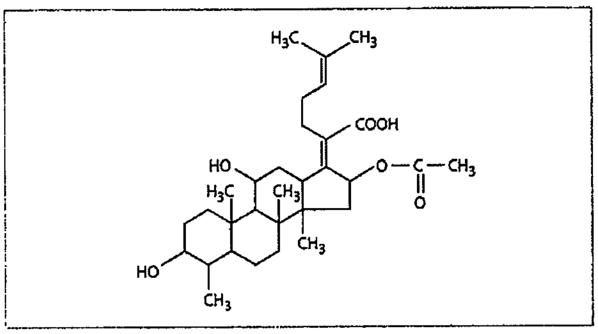
D. Greenwood

The fusidanes are steroid-like antibiotics with a basic cyclopentanophenanthrene structure. Their stereochemistry differs from that of metabolically active steroids and they do not exert any hormonal or anti-inflammatory activity. The group includes helvolic acid, cephalosporin P_1 and fusidic acid. Helvolic acid, a product of *Aspergillus fumigatus*, attracted some early attention because of its weak antimycobacterial activity; cephalosporin P_1 was a component of the antibiotic complex of the mold that also yielded the first true cephalosporin.

Fusidic acid, is much the most active member of the group and is the only one commercially available. It was discovered in Denmark in 1960 as a product of a fungus originally isolated in Japan from monkey dung. The principal interest of fusidic acid lies in its antistaphylococcal activity.

FUSIDIC ACID

Molecular weight (sodium salt): 538.7.



A fermentation product of *Fusidium coccineum*. Supplied as the sodium salt, which is readily soluble in water, or suspension of the acid. Intravenous preparations (sodium or diethanolamine salt) are dissolved in phosphate–citrate buffer. Several formulations are available for topical application. The dry powder is stable for 3 years.

Antimicrobial activity

Fusidic acid is active against most Gram-positive bacteria, but all aerobic Gram-negative negative bacilli are resistant (Table 21.1). Streptococci and pneumococci are much less susceptible than staphylococci. *Bacteroides fragilis*, *Nocardia asteroides* (MIC 0.5–4 mg/l) and *Corynebacterium diphtheriae* (MIC <0.01 mg/l), *Clostridium* spp. (MIC 0.01–0.5 mg/l) are susceptible. It is moderately active against many mycobacteria, including *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium malmoense* and *Mycobacterium leprae*, but other mycobacteria are resistant. Fusidic acid shows some activity against certain protozoa, including *Giardia lamblia* and *Plasmodium falciparum*.

In 50% serum, the MIC may double and it is slightly more effective at pH 6–7 than at pH 8. It is bactericidal in concentrations close to the MIC.

Interaction with penicillins is complex. Against some strains of staphylococci synergy occurs, but others show two-way antagonism or 'indifference'. There is no useful synergy with other antistaphylococcal agents.

Table 21.1 Activity of sodium fusidate against some common pathogenic bacteria

Species	MIC (mg/l)
Staphylococcus aureus	0.03–0.1
Streptococcus pyogenes	4–16
Streptococcus pneumoniae	2–16
Enterococcus faecalis	1–4
Neisseria spp.	0.03–1
Escherichia coli	R
Klebsiella pneumoniae	R
Pseudomonas aeruginosa	R
Bacteroides fragilis	2
Mycobacterium tuberculosis	8–32

R, resistant (MIC >64 mg/l)

Acquired resistance

Large inocula of most strains of *Staph. aureus* contain a small number of resistant mutants, which emerge rapidly in vitro and sometimes during therapy. The growth rate, coagulase, hemolysin and β-lactamase production of these mutants appear to be unimpaired. Despite the ease of emergence of resistance in vitro, resistance remains rare in clinical isolates (1–2%) and is mostly plasmid mediated. Although topical applications are liable to facilitate the emergence of resistant mutants, extensive use of the drug on the skin does not seem to have added significantly to the pool of resistant strains in circulation.

Resistance in staphylococci is usually due to chromosomal mutation, which results in a change at the target site (elongation factor G). Plasmid-mediated resistance also occurs and appears to be associated with drug exclusion. Genes for β-lactamase and sodium fusidate resistance are commonly carried on the same plasmid.

Antistaphylococcal penicillins prevent the emergence of fusidic acid-resistant mutants of *Staph. aureus*. In addition, the effect of fusidic acid on protein synthesis may prevent generation of sufficient β-lactamase to destroy penicillin.

Pharmacokinetics

Oral absorption: sodium salt suspension	>90% 70%
C_{max}: 500 mg oral 500 mg i.v.	30 mg/l after 2–3 h 50 mg/l end-infusion
Plasma half-life	c 9 h
Volume of distribution	c. 12 l
Plasma protein binding	97%

Absorption

Fusidic acid suspension is less well absorbed than the sodium salt of the tablet formulation. In children absorption is more rapid than in adults. Milk appears to delay absorption, peak concentrations not being reached for 4–8 h. Because of slow elimination, considerable accumulation of the drug occurs on repeated administration of both oral and intravenous formulations.

Distribution

Sodium fusidate is well distributed in the tissues and most organs of the body. It does not reach the cerebrospinal fluid, but penetrates into cerebral abscesses. Inhibitory levels are obtained in muscle, kidney, lungs and pleural exudate. Bone concentrations in samples taken at operation from patients with chronic osteomyelitis treated for at least 5 days were 1.7–14.9 mg/g in patients receiving 1.5 g/day and 3.4–14.8 mg/g in patients receiving 3 g/day.

Levels in excess of 7 mg/l have been found in aspirated synovial fluid from patients with osteo- or rheumatoid arthritis after 3–7 days' treatment with 0.75 or 1.5 g/day. The drug has been detected in brain, milk and placenta, which it crosses to reach the fetus. In patients treated with 1.5 g/day, levels of 0.08–0.84 mg/l were found in the aqueous humor after 1 day and 1.2–2.0 mg/l after 3 days' treatment. In the post-distribution phase, about half of the drug is in the peripheral compartment, in keeping with the known ability of sodium fusidate to penetrate into tissues including bone.

Metabolism and excretion

It is extensively metabolized in the liver and is excreted in the bile in the form of glucuronides and various other metabolites. Only about 2% of the administered dose can be recovered in active form in the feces. Less than 1% of active antibiotic is excreted in the urine. Very little of the drug is removed by dialysis.

Toxicity and side effects

Oral sodium fusidate has been administered for prolonged periods for the control of chronic staphylococcal sepsis without mishap. Mild gastrointestinal disturbance and occasional rashes have been reported. Some patients develop abnormalities in liver function tests and jaundice which resolve on withdrawal of therapy. Jaundice is less common with oral than with parenteral therapy. The drug is not recommended in hepatic insufficiency. Rapid infusion of diethanolamine fusidate may lead to venospasm or thrombosis, and occasionally to hypocalcemia, possibly as an effect of the buffer.

Clinical use

Systemic formulations

- Severe staphylococcal infections, particularly bone and joint infections (in combination with penicillins, erythromycin or clindamycin).
- Infection with methicillin-resistant staphylococci (including endocarditis).
- Prosthetic valve endocarditis due to 'diphtheroids' (in combination with erythromycin).

Topical formulations

- Skin infections, principally those involving staphylococci, but including erythrasma.
- Acute staphylococcal conjunctivitis.

In addition to its antibacterial activity, fusidic acid possesses immunomodulatory properties by stimulation of T cells and interference with cytokine production. This has led to the suggestion that it might be of value in the treatment of several non-bacterial conditions, including Crohn's disease and autoimmune diabetes.

Preparations and dosage

Proprietary name: Fucidin.

Preparations: Tablets, suspension, injection, topical preparations.

Dosage: Adults, oral (as sodium fusidate): 500 mg every 8 h, doubled for severe infections. Children (as fusidic acid) ≤1 year, 50 mg/kg per day in three divided doses; 1–5 years, 250 mg every 8 h; 5–12 years, 500 mg every 8 h.

Intravenous infusion (as sodium fusidate): adults >50 kg, 500 mg three times daily; adult <50 kg and children, 6–7 mg/kg three times daily.

Widely available (not USA).

Further information

Franzblau SG, Biswas AN, Harris EB 1992 Fusidic acid is highly active against extracellular and intracellular *Mycobacterium leprae. Antimicrobial Agents and Chemotherapy* 36: 92–94.

Nicoletti F, Di Marco R, Conget I et al 2000 Sodium fusidate ameliorates the course of diabetes induced in mice by multiple low doses of streptozotocin. *Journal of Autoimmunity* 15: 395–405.

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